Summary of Safety and Effectiveness Data

Novacor® Left Ventricular Assist System

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– *Summary of Safety and Effectiveness Data*
Novacor® Left Ventricular Assist System
Baxter Healthcare Corporation

1 General Information

Device Generic Name:	Left Ventricular Assist System
Device Trade Name:	Novacor® LVAS
Applicant's Name and Address:	Baxter Healthcare Corporation Novacor Division 7799 Pardee Lane Oakland, CA 94621
PMA Number:	P980012
Date of Notice of Approval to Applicant:	September 29, 1998

2 Indications and Usage

The LVAS is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. The LVAS is indicated for use both inside and outside of the hospital.

3 Contraindications

The LVAS is contraindicated for use in patients with:

- Primary coagulation or platelet disorder
- Body surface area less than $1.5m^2$ or greater than $2.5m^2$.

4 Warnings and Precautions

See WARNINGS AND PRECAUTIONS in the final draft labeling (Information for Use)

5 Device Description

The Novacor® LVAS (LVAS), an implanted electronic left ventricular assist system, operates in series with the left ventricle (LV) to provide circulatory support by taking over most of the work of the native LV. There are five major components that, when integrated, form the LVAS: the Implant, Compact Controller, Power Packs (Primary and Reserve), LVAS Monitor and Personal Monitor.

The Implant, the implanted portion of the LVAS, consists of an integrated Pump/Drive Unit with a percutaneous lead carrying the control and power leads, bioprosthetic Valved Conduits, an Inflow Conduit and an Outflow Conduit. The device is implanted anteriorly within the left upper

quadrant of the abdomen. The pump Inflow Conduit pierces the pericardial portion of the diaphragm to receive blood from a cannula inserted, via the apex, into the left ventricular cavity. The Outflow Conduit is anastomosed to the aorta.

The Compact Controller located extracorporeally, controls the timing of pump operation based on preprogrammed control algorithms and adjustable control parameters. In addition, the Compact Controller monitors LVAS operation and activates alarms. It is intended to be worn on a belt around the recipient's waist, or carried in a shoulder bag or in the pockets of a special vest. Together, the implant and the Compact Controller for the core of the LVAS. Power to the Compact Controller is provided from two power sources – a main power source (primary power pack, LVAS monitor or Personal Monitor) and a secondary power source (Reserve Power Pack).

6 Alternative Practices or Procedures

There are currently three methods available for treating patients in end stage cardiac disease with nonreversible left ventricular failure while awaiting transplantation: pharmacologic agents to enhance cardiovascular function, intra-aortic balloon pumps for short term mechanical circulatory support, and other commercially available electromechanical ventricular assist devices

7 Marketing History

The LVAS has been exported to 17 countries, including Argentina, Australia, Belgium, Canada, People's Republic of China, Czech Republic, France, Germany, Italy, Japan, Netherlands, Norway, Russia, Spain, Sweden, Switzerland, and the United Kingdom.

The LVAS has not been withdrawn from any country for any reasons related to the safety or effectiveness of the device.

8 Adverse Events

8.1 Observed Adverse Events

Adverse events were collected for all patients enrolled in the clinical study of the device, which included 156 cardiac transplant candidates and 35 control patients at 22 medical centers. The occurrence of each of the 16 most frequent adverse events that occurred in the clinical trials is presented in Table 8-1

Table 8-1 Summary of Adverse Event Data

	LVAS Patients (N=156)			Control Patients (N=35)		
Adverse Event Type	# of Patients	% Patients (95% CI)	# of Events	# of Patients	% Patients (95% CI)	# of Events
Bleeding	62	39.7% (32.0%, 47.9%)	102	0	0.0% (N/A)	0
Blood Pump/Drive Failure	1	0.6% (0.0%, 3.5%)	1	N/A	N/A (N/A)	N/A
Cardiac Tamponade	26	16.7% (11.2%, 23.5%)	31	0	0.0% (N/A)	0
Cardiovascular Dysfunction	53	34.0% (26.6%,42.0%)	69	26	74.3% (56.7%, 87.5%)	50
Control System Failure	0	0.0% (N/A)	0	N/A	N/A (N/A)	N/A
Embolism (CNS)	42	26.9% (20.1%, 34.6%)	61	0	0.0% (N/A)	0
Embolism (Non-CNS)	23	14.7% (9.6%, 21.3%)	39	8	22.9% (10.4%, 40.1%)	11
Hemolysis	1	0.6% (0.0%, 3.5%)	1	0	0.0% (N/A)	0
Hepatic Dysfunction	59	37.8% (30.2%, 45.9%)	63	8	22.9% (10.4%, 40.1%)	8
Infection	103	66.0% (58.0%, 73.4%)	195	16	45.7% (28.8%, 63.4%)	26
Neurologic Deficit	64	41.0% (33.2%, 49.2%)	96	3	8.6% (1.8%, 23.1%)	5
Other[1]	47	30.1% (23.1%, 38.0%)	68	6	17.1% (6.6%, 33.6%)	13
Renal Dysfunction	42	26.9% (20.1%, 34.6%)	47	15	42.9% (26.3%, 60.6%)	15
Reoperation	74	47.4% (39.4%, 55.6%)	146	10	28.6% (14.6%, 46.3%)	11
Respiratory Dysfunction	53	34.0% (26.6%, 42.0%)	63	14	40.0% (23.9%, 57.9%)	22
Right Ventricular Dysfunction	16	10.3% (6.0%, 16.1%)	16	5	14.3% (4.8%, 30.3%)	5

The out of hospital (OOH) LVAS patients were on the device longer (mean 4.5 months) than the in-hospital (IH) LVAS patients (mean 1.6 months), the linearized rates for the adverse events are presented in Table 8-2.

[1] The "other" category includes all other adverse events not specifically defined in this study. Some examples are adverse drug reactions, chest tube insertion, wound debridement, slow continuous ultrafiltration for volume removal, ischemic bowel unrelated to embolism, elevated panel reactive antibodies and pulmonary edema.

Table 8-2. In-hospital and Out-of-hospital Adverse Events for LVAS Patients

	IH (N = 101)				OOH[1] (N = 55)			
Adverse Event Type	% of Patients	Linearized Rate (event/ month)	Upper One-tailed 95% CL	# of Events	% of Patients	Linearized Rate (event/ month)	Upper One-tailed 95% CL	# of Events
Bleeding	36.6%	0.341	0.426	55	1.8 %	0.006	0.033	1
Blood Pump/Drive Failure	0.0%	0.000	0.019	0	1.8 %	0.006	0.033	1
Cardiac Tamponade	15.8%	0.112	0.164	18	0.0 %	0.000	0.019	0
Cardiovascular Dysfunction	31.7%	0.260	0.336	42	14.5 %	0.051	0.091	8
Control System Failure	0.0%	0.000	0.019	0	0.0 %	0.000	0.019	0
Embolism (CNS)	16.8%	0.174	0.237	28	27.3 %	0.121	0.176	19
Embolism (Non-CNS)	3.0%	0.019	0.048	3	0.0 %	0.000	0.019	0
Hemolysis	0.0%	0.000	0.019	0	0.0 %	0.000	0.019	0
Hepatic Dysfunction	33.7%	0.217	0.287	35	1.8 %	0.006	0.033	1
Infection	60.4%	0.688	0.804	111	30.9 %	0.172	0.235	27
Neurologic Deficit	37.6%	0.316	0.398	51	29.1 %	0.165	0.228	26
Other	26.7%	0.223	0.294	36	10.9 %	0.038	0.075	6
Renal Dysfunction	27.7%	0.192	0.258	31	1.8 %	0.006	0.033	1
Reoperation	47.5%	0.570	0.677	92	14.5 %	0.076	0.123	12
Respiratory Dysfunction	32.7%	0.248	0.322	40	5.5 %	0.019	0.049	3
Right Ventricular Dysfunction	3.0%	0.019	0.048	3	0.0 %	0.000	0.019	0

8.2 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with the use of a ventricular assist device (including those listed above).

- Bleeding
- Death
- Hepatic Dysfunction
- Infection
- Neurological Dysfunction
- Pulmonary Dysfunction
- Renal Dysfunction
- Reoperation
- Right Heart Failure
- Thromboembolism
- Wound dehiscence

9 Summary of Pre-Clinical Studies

9.1 Biocompatibility Testing

In vitro and *in vivo* biocompatibility studies were performed on all materials with direct tissue or fluid contact. The studies were performed in accordance with *International Standards*

[1] Presents events occurring after first discharge and/or excursion

Organization (ISO) 10993-1-1994 Biological Evaluation of Medical Devices - Part 1: Guidance on Selection of Tests, and the *FDA Office of Device Evaluation General Program Memorandum No. G95-1.* All materials with direct tissue or fluid contact were considered biocompatible.

9.2 *In Vivo Studies*

A series of *in vivo* animal studies were performed on the LVAS to assess system reliability, pump operation, hemodynamic stability, organ function, and pathology.

In total, 12 LVAS were implanted in 12 male young adult sheep (1-2 years old, weight range 65-95 kg) for periods up to 275 days. The animals demonstrated no clinical signs indicative of device failures or other device-related abnormalities. Clinical pathological studies as well as gross and histopathologic examinations of the animals and the devices demonstrated no abnormalities related to device function. Additionally, there was no evidence in any of the organ samples, pump pocket, or percutaneous driveline site of damage associated with leachable materials, dislodgment and embolization of device particulates, or changes indicative of thermal damage. Specific analyses related to device performance indicated that the device performed as intended in the animal recipients.

9.3 *In Vitro System Testing*

Extensive laboratory testing was performed on the LVAS to demonstrate that it met its intended functional requirements as defined in the product specifications and risk analysis.

The testing was designed to challenge the LVAS as an integrated system and each major element of the system, i.e. Implant, Compact Controller, Power Packs, LVAS Monitor, and Personal Monitor. The tables which follow summarize the testing and the results.

Table 9-1. Verification and Validation of the Integrated System

Test Description	Test Results
System performance. Testing was performed to verify physiologic operating conditions, LVAS operating range, pump output, and outflow pulse in all control modes, at the extremes of physiologic conditions, at all extremes of control misadjustment, and at all extremes of the intended operating conditions.	Testing demonstrated that operating parameters are within specification.
Display accuracy. Testing was performed to verify the accuracy of pump rate, pump outflow, and pump fill and eject rate values displayed by the monitors.	Testing demonstrated that the display parameters are within specification.
Alarms. Testing was performed to verify that an alarm signal will occur when a defined out-of-limit or fault condition is detected, and to verify the alarm volume.	Testing at both at the integrated system level and at the subsystem level demonstrated that the alarm functions met specification.
Interconnections. Testing was performed to verify retention force and electrical integrity following insertion/withdrawal cycling.	Testing demonstrated that each connector/receptacle pair met specification.
Human factors. Testing was performed to verify the safety and usability of the system.	A comprehensive human factors assessment was performed by the American Institutes of Research (AIR). Testing demonstrated that the LVAS reflects a high level of engineering and design quality.
Environmental Limits and Packaging. Testing was performed to verify that the implant kit packaging remains intact and provides appropriate protection after being subjected to sterilization, temperature preconditioning, and simulated shipping and handling. Packaged systems were exposed to simulated shipping and distribution conditions. Unpackaged external components were exposed to drop, shock, vibration, temperature, and humidity.	Testing demonstrated that the implant kit packaging maintains the integrity of the sterile barrier and preserves the functional integrity of the components. that the packaged external subsystems met performance specification; and that the unpackaged external subsystems met performance specification.
Electrical safety and electro-magnetic compatibility. Testing was performed to verify conformance with UL2601-1. Dielectric withstand and leakage current were measured in accordance with IEC 60601-1/UL2601-1. The system was tested to the requirements of CISPR 11 for radiated and conducted EMI emissions; IEC 60601-1-2 (1993) for radiated RF, electrostatic discharge, and transients and surges and included additional testing for immunity to conducted RF, voltage variations and interruptions, and magnetic fields; ESU and Defibrillator EMI immunity.	Testing demonstrated conformance to applicable standards.

Table 9-2. Verification and Validation of the Implant

Test Description	Test Results
Pumping performance. Testing was performed to verify static performance of the pressure/volume profile during ejection, pump pressure during filling, and full-fill stroke volume; and to demonstrate dynamic performance of the pump stroke volume versus afterload (ejection performance), pump output versus preload and afterload (filling and ejection performance) and range of pump rates.	Testing was performed on a mock circulatory loop. configured to provide a constant filling pressure (preload). The system was operated over a matrix of preloads and afterloads while pump output, stroke volume and rate were measured and shown be within specification.
Valved conduits. Testing was performed to verify the hydrodynamics, porosity, durability, and physical attributes.	Testing demonstrated that performance parameters are within specification.
Conduits. Testing was performed to verify the tensile strength of the conduit assembly, burst strength and porosity of the graft material, and physical attributes.	Testing demonstrated that performance parameters are within specification.
Seals and encapsulation. Testing was performed to verify seals between the Pump/Drive Unit and the Valved Conduits, and the seals between the Valved Conduits and the Inflow/Outflow Conduits, and the encapsulation seal of the Pump/Drive Unit.	Testing demonstrated that the interface seals and the encapsulation seal are within specification.
Percutaneous Lead. Testing was performed to verify the pneumatic pressure drop over a range of airflow rates and to demonstrate durability of the Lead from bending and torsional fatigue, and tensile loading.	Testing demonstrated that the pressure drops, fatigue resistance, and tensile strength are within specification.
Sterility. Testing was performed to verify a Sterility Assurance Level of 10^{-6} for implantable components.	Testing demonstrated that parameters are within specification.
Structural analysis. Testing was performed to verify fatigue strength, bond strength, wear resistance, and durability of the Pump/Drive Unit.	Testing demonstrated that performance parameters are within specification.
Flow visualization. Testing was performed to verify the flow patterns and pump washing.	Testing demonstrated that performance parameters are within specification.
Shelf life. Testing was performed to verify the package (sterility) integrity and product (functional) integrity over time for the Pump/Drive Unit, Valved Conduits, and Inflow/Outflow Conduits.	Testing demonstrated that parameters are within specification, i.e., a two year shelf life.

Table 9-3. Verification and Validation of the Compact Controller

Test Description	Test Results
General Performance. Testing was performed to verify the closure servo control range, beat rate, position sensor accuracy, and power consumption.	Testing demonstrated that performance parameters are within specification.
Power Handling Characteristics. Testing was performed to verify the quiescent controller power, input DC voltage range, capacitor charge voltage limit, and low voltage latching current were verified.	Testing demonstrated that performance parameters are within specification.
Power Sense Lead Signals. Testing was performed to verify the pulse amplitude that the Compact Controller detects and the sense lead voltage at various loads.	Testing demonstrated that performance parameters are within specification.
Serial Communication Baud Rate. Testing was performed to verify the communication of data and the baud rate.	Testing demonstrated that performance parameters are within specification.
Compact Controller Software. Testing was performed to verify the alarms and all other software functions.	Testing demonstrated that the software function was acceptable.

Table 9-4. Verification and Validation of the Power Packs and Charger

Test Description	Test Results
Power Characteristics. Testing was performed to verify the cycle life, nominal run time, nominal recharge time, and voltage. Additionally, the self-discharge time was verified in the Reserve Power Pack.	Testing demonstrated that performance parameters are within specification.
Sense Lead and Charger Control. Testing was performed to verify the detection of a connection to either a Power Pack Charger or Compact Controller, charge current requesting.	Testing demonstrated that performance parameters are within specification.
Software. Testing was performed to verify the alarms and all other software functions.	Testing demonstrated that the software function was acceptable.
Power Characteristics. Testing was performed to verify the input voltage range, output voltage range, and output current range.	Testing demonstrated that performance parameters are within specification.
Control Circuit. Testing was performed to verify the control threshold battery voltage, default current, charge current accuracy and limits, and sense lead voltage.	Testing demonstrated that performance parameters are within specification.

Table 9-5. Verification and Validation of the LVAS Monitor and Personal Monitor	
Test Description	Test Results
Power Supply. Testing was performed to verify the AC input current and DC output voltage.	Testing demonstrated that performance parameters are within specification.
Display Resolution And Accuracy. Testing was performed to verify the display resolution and heart rate accuracy (LVAS Monitor) and the Standby Power Source estimated runtime accuracy (Personal Monitor).	Testing demonstrated that performance parameters are within specification.
Sense Lead Operations. Testing was performed to verify the frequency and voltage of the sense lead under various conditions.	Testing demonstrated that performance parameters are within specification.
Internal Battery. Testing was performed to verify the rundown and recharge times.	Testing demonstrated that performance parameters are within specification.
Standby Power Source. (Personal Monitor only.) Testing was performed to verify the accuracy of runtime and temperature sensors and of the rundown time algorithm.	Testing demonstrated that performance parameters are within specification.
ECG Subsystem. (LVAS Monitor only.) Testing was performed to verify the display of the heart rate and ECG waveform.	Testing demonstrated that performance parameters are within specification.
LVAS Monitor Software. Testing was performed to verify the alarms and all other software functions.	Testing demonstrated that the software function was acceptable.

Reliability

An in vitro study was performed on the LVAS to demonstrate system reliability and durability. Twelve units, submerged in normal saline at body temperature, were subjected to varying simulated load conditions using mock circulatory loops. The 12 units have all exceeded 3 years of test without failure. Testing is ongoing. As of September 1998, the cumulative test duration is 49 years with an average system duration of 4.1 years (with a range of 3.4 to 4.9 years Table 9-6 shows the multi-year reliability calculated according to a Weibull model for an 80% confidence.

Table 9-6. In Vitro Reliability (80% confidence)

1 Year	2 Year	3 Year
99.9%	98%	86%

The cumulative implant duration for the 129 LVAS patients who met all entrance criteria was 10,374 patient-days (28.4 patient-years) with a mean duration of 80 ± 83 days (± S.D.) and a range of 1 - 657 days. There was a single pump/drive failure and no control system failures. The pump/drive unit failure resulted from damage to the external portion of the Percutaneous Lead, after an implant duration of 465 days.

10 Summary of Clinical Studies

10.1 Objectives

The LVAS was studied as a bridge to cardiac transplantation in a multicenter, non-randomized, concurrent control clinical trial. The primary objective of the clinical trial was to show an improved survival, with acceptable neurological function, and improved hemodynamics, at 30 days post-transplant.

10.2 Methods

Cardiac transplant patients in imminent danger of death were implanted with the LVAS with the intent of maintaining them as viable transplant candidates until donor hearts became available.

To be considered a trial success, a patient, at 30 days after transplantation, must have survived with acceptable neurological function, be NYHA Functional Class III or better, and have had an average pump index of 2.0 L/min/m^2 or greater during the period of LVAS support.

10.3 Description of Patients and Gender Bias

Between March, 1996, and June, 1998, a total of 191 patients were enrolled in the study (156 patients implanted with the device and 35 CONTROL patients) at 22 clinical sites. Patients with New York Heart Association (NYHA) Functional Class IV heart failure who were United Network for Organ Sharing (UNOS) Status I candidates for cardiac transplantation, 14 to 68 years old, were included in the study. Of the 156 patients implanted with the device, 129 were subsequently found to have met all inclusion/exclusion criteria and were designated as CORE LVAS patients. Implant duration for the CORE LVAS patients ranged from 1 to 657 days with a mean of 80 ± 83 days (mean ± S.D.). The other 27 patients were designated as non-CORE LVAS patients. The CORE patients formed the basis of effectiveness analyses while the CORE + non-CORE patients were included in the analyses of adverse events. CONTROL patients met the same criteria as CORE LVAS patients, but were treated with conventional medical therapy because either a device was not available or they chose not to accept a device.

Inclusion and exclusion criteria were designed and the study was conducted to avoid gender bias in patient enrollment. Of the 129 CORE LVAS patients 108 (83.7%) were male and 21 (16.7%) were female which is consistent with the UNOS Registry for Status I candidates.

10.4 Results

Of the 129 CORE LVAS patients, 104 had reached trial endpoint as of June 1998. Table 10-1 shows survived to transplant and trial success.

Table 10-1. Survival to Transplant and Trial Success
Patients evaluable at 30 days post-transplant, N=139

Endpoint	Core LVAS (N=104)	Control (N=35)	Difference [95% CI]
Transplant	78% (81/104)	37% (13/35)	41%* [23%, -59%]
Trial success	67% (70/104)	34% (12/35)	29%* [15%, -51%]

CI = 95% confidence interval by normal approximation

* Difference statistically significant ($p<0.001$) by Fisher's Exact Test

The hemodynamic performance of the LVAS was assessed through a comparison of pre- and post-implant values of cardiac index, mean systemic arterial pressure, and pulmonary artery diastolic pressure. For the CORE LVAS population, the cardiac index (obtained by averaging each individual patient's averaged pump index) was 2.8 ± 0.04 L/min/m^2, compared to the pre-implant cardiac index of 2.0 ± 0.05 L/min/m^2. Mean systemic arterial pressure increased from 69 $\pm$ 1.0 mmHg to 83 $\pm$ 0.8 mmHg, while pulmonary artery diastolic pressure decreased from 28 $\pm$ 0.6 mmHg to 19 $\pm$ 0.5 mmHg as early as one day post implantation. For the CORE LVAS patients, the measured indices for renal and hepatic function (serum creatinine, blood urea nitrogen, total bilirubin) and the liver transaminases (SGOT and SGPT), returned to within normal limits during LVAS support.

The actuarial survival estimate (Kaplan-Meier) at one-year post transplantation for CORE LVAS patients is 78% and 85% for the CONTROL patients. Of the 104 CORE LVAS patients, 81 were transplanted. Of the 81, 33 survived to one year, 12 did not survive and 36 are alive but did not reach the one-year endpoint. Of the 35 CONTROL patients, 13 were transplanted, of the 13, 11 survived to one year, 2 did not survive.

Table 10-2. Actuarial Survival Post-Transplant
Patients evaluable at one year, N=94

Kaplan-Meier Survival	Core LVAS (N=81)	Control (N=13)	Difference [95% CI]
1 year post-transplant	78%	85%	7% [-30%, 16%]

Data on hematologic stability indicates that hemoglobin, hematocrit and red blood cell counts initially decreased postimplant. However, these changes were transient and returned to preimplant values.

Out-of-Hospital Patients: Of the 156 LVAS patients, 55 (35%) were discharged from the hospital and/or took excursions while awaiting transplantation [defined as Out-Of-Hospital (OOH)], the remaining 101 patients did not leave the hospital [defined as In-Hospital (IH)].

Of the 101 IH patients, 24 had not reached a trial endpoint as of June 1998, yielding 77 patients for the calculation of survival and success. Of the 77 patients, 51 (66%) survived to transplant and 39 (51%) met all success criteria.

Among the 55 OOH patients, 45 (82%) were discharged and 10 (18%) took occasional excursions but were not discharged. On average, these patients began taking excursions at 49.2 days postimplant. Of the 55 patients, 7 had not reached a trial endpoint as of June 1998, yielding

48 for the calculation of survival and success. Of the 48, 42 (88%) survived to transplant and 36 (75%) met all success criteria.

Table 10-3 summarizes the survival and success rates for both the OOH and the IH patients.

Table 10-3. Transplant and Trial Success for IH and OOH Experience
Core patients evaluable at 30 days post-transplant, N=125

Endpoint	IH Patients (N=77)	OOH patients (N=48)	Difference [95% CI]
Transplanted	66% (51/77)	88% (42/48)	-21% [-35%, -7%]
Trial success	51% (39/77)	75% (36/48)	-24% [-41%, -8%]

CI = 95% confidence interval by normal approximation

11 Conclusions Drawn from the Studies

Preclinical *in vitro* studies demonstrated that the LVAS conforms to the system design, and that the design meets the intended user requirements.

Data from the multicenter clinical trial show treatment with the circulatory support, improved hemodynamics and an increased survival in cardiac transplant candidates, when compared to those patients who were maintained with conventional medical therapy.

12 Panel Recommendation

Pursuant to section 515(c)(2) of the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

13 FDA Decision

FDA performed an inspection and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

14 Approval Specifications

Directions for Use: See Final Draft Labeling (Information for Use)

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the labeling.

Post-approval Requirements and Restrictions: See Approval Order